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Copper-Catalyzed Synthesis of Alkyl-Substituted Pyrrolo[1,2-*a*]-quinoxalines from 2-(1*H*-Pyrrol-1-yl)anilines and Alkylboronic Acids

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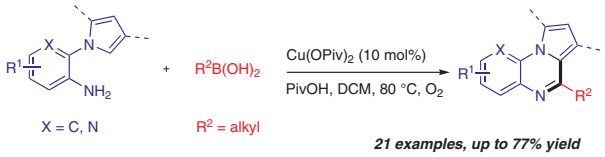

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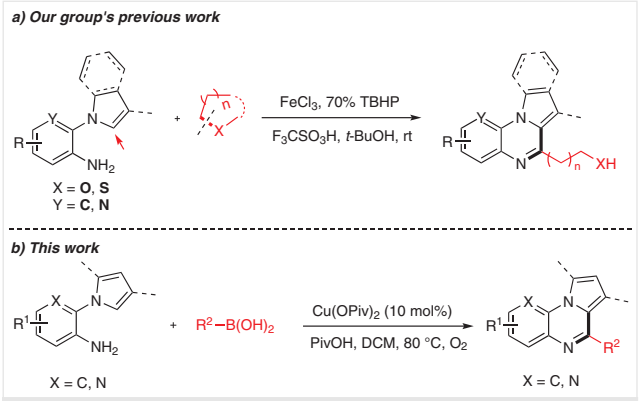
Abstract A radical pathway for the construction of pyrrolo[1,2-*a*]quinoxalines by using 2-(1*H*-pyrrol-1-yl)anilines and alkylboronic acids has been developed. Features of this process include Cu catalysis, readily accessible starting materials, and simple operations. Alkylboronic acids are used for the construction of pyrrolo[1,2-*a*]quinoxaline derivatives, and the desired products are obtained in moderate yields.

Key words pyrrolylanilines, alkylboronic acids, pyrroloquinoxalines, radical reaction

The pyrrolo[1,2-*a*]quinoxaline skeleton is an important scaffold in various compounds and in synthetic intermediates with biological activities.[1] Some pyrrolo[1,2-*a*]quinoxaline derivatives have been found to have potential pharmacologically activities, such as anticancer activity,[2] affinity toward 5-hydroxytyrosine receptors,[3] and in vitro antiparasitic activity.[4] Because of their wide range of applications, pyrrolo[1,2-*a*]quinoxaline derivatives have attracted considerable attention, and various novel synthetic methods have been developed to build this framework. In 1965, Cheeseman and Tuck reported a related method for synthesizing pyrrolo[1,2-*a*]quinoxalines from (1*H*-pyrrol-1-yl)anilines.[5] Recently, Ma and co-workers proposed a convenient synthesis of pyrrolo[1,2-*a*]quinoxaline derivatives from simple substrates.[6] Jiang and co-workers described a cyclization of (1*H*-pyrrol-1-yl)anilines with alkyl alcohols to give pyrrolo[1,2-*a*]quinoxalines in good yields.[7] In 2014, Jamison and co-workers reported a one-pot reaction of 1-(2-isocyanophenyl)-1*H*-pyrrole with visible-light photoredox catalysis for the synthesis of pyrrolo[1,2-*a*]quinoxalines.[8] de Fatima Periera and Thiéry also reported a synthesis of pyrrolo[1,2-*a*]quinoxalines from 1-(2-nitrophenyl)-1*H*-pyrrole in the presence of Fe(0) and HCl.[9] Our group previously developed protocols for the synthesis the pyrrolo[1,2-*a*]quinoxalines containing hydroxyalkyl or cyanoalkyl groups through a tandem ring-opening/cyclization reaction (Scheme 1).[10]



Scheme 1 Syntheses of pyrrolo[1,2-*a*]quinoxaline derivatives

Alkylboronic acids, as useful substrates in coupling reactions, have been widely studied. However, compared with trialkylboranes or organotrifluoroborates, organoboronic acids are rarely used as radical precursors to construct C–C bonds.[11] Although several transition-metal-catalyzed radical cascade reaction of boronic acids through radical pathways have been developed, the use of organoboronic acids as radical precursors to construct heterocyclic scaffolds is rare and challenging.[12] We therefore hypothesized that alkyl moieties might be introduced into pyrrolo[1,2-*a*]quinoxalines by starting from alkylboronic acids and 2-(1*H*-pyrrol-1-yl)anilines. Here we report the development of a method for building alkyl-substituted pyrrolo[1,2-*a*]quinoxalines from 2-(1*H*-pyrrol-1-yl)anilines and alkylboronic acids through a copper-catalyzed cyclization reaction (Scheme 1).

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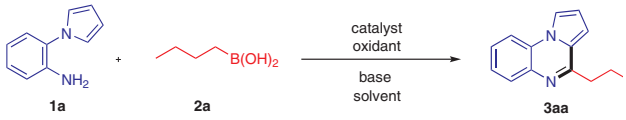
To test our hypothesis, we attempted to react 2-(1*H*-pyrrol-1-yl)aniline (**1a**) and butylboronic acid (**2a**) as model substrates in the presence of $Cu(OPiv)_2$ (10 mol %) and PivOH (1 equiv) with stirring at 70 °C for 12 hours in NMP under an O_2 atmosphere (Table 1). The desired product **3aa** was obtained in 43% yield. Then, several solvents were examined (Table 1, entries 2–5), among which dichloromethane was found to be the most effective (entry 4). Subsequently, a screening of transition-metal catalysts was performed and $Cu(OPiv)_2$ was found to be more effective than CuI, $CuCl_2$, $FeCl_3$, or $Pd(OAc)_2$ in this reaction (entries 4 and 6–9). Furthermore, when the temperature was changed, an enhancement in the product yield was observed at 80 °C (entries 4 and 12–14). No significant increase in yield was observed when other acids were used instead of PivOH (entries 14–17). Finally, the optimal outcome was obtained by using the conditions shown in entry 13.

With the optimized reaction conditions in hand, we started to investigate the scope of the 2-(1*H*-pyrrol-1-yl)aniline in this reaction, and the results are summarized in Table 2. Substrates **1b–e** with electron-donating groups afforded the desired products **3ba–ea** in good yields. Moreover, substrates **1f–m** bearing electron-withdrawing groups such as F, Cl, Br on the phenyl ring of the N-heterocycle reacted smoothly with butylboronic acid to give the desired products in yields of 55–77%. To our delight, the substituted 2-(1*H*-pyrrol-1-yl)pyridin-3-amines **1n–p** reacted smoothly with **2a** to give the corresponding products **3na–pa** in yields of 22–29 %.

Table 1 Optimization of the Reaction Conditions[a]

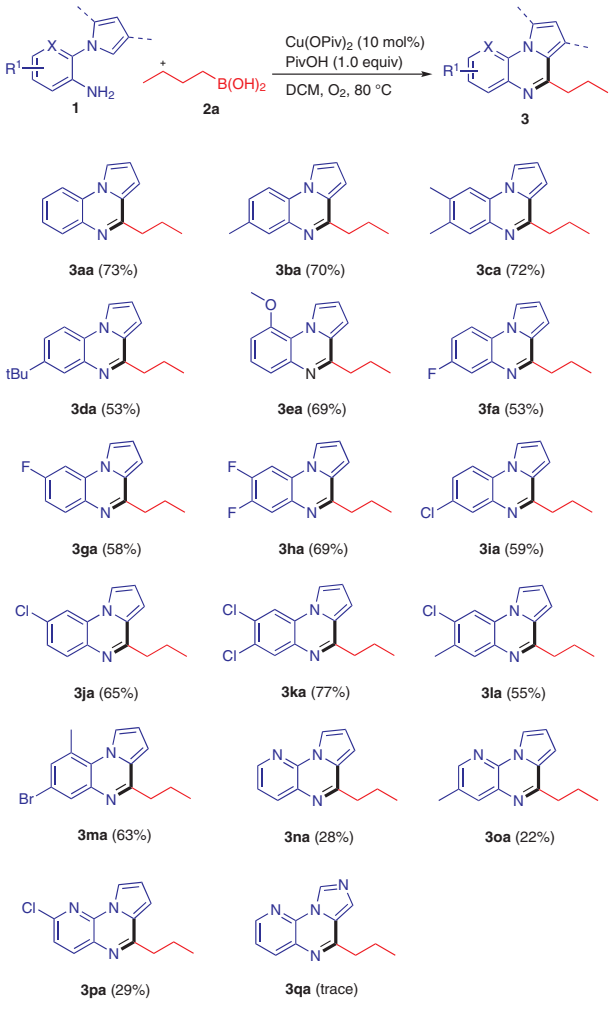


1a 2a 3aa

Entry	Catalyst	Oxidant (equiv)	Solvent	Temp (°C)	Acid	Yield[b] (%)
1	$Cu(OPiv)_2$	O_2	NMP	70	PivOH	43
2	$Cu(OPiv)_2$	O_2	AcOH	70	PivOH	13
3	$Cu(OPiv)_2$	O_2	DMSO	70	PivOH	0
4	$Cu(OPiv)_2$	O_2	DCM	70	PivOH	71
5	$Cu(OPiv)_2$	O_2	PhCl	70	PivOH	64
6	CuI	O_2	DCM	80	PivOH	67
7	$CuCl_2$	O_2	DCM	80	PivOH	39
8	$FeCl_3$	O_2	DCM	80	PivOH	3
9	$Pd(OAc)_2$	O_2	DCM	80	PivOH	7
10	$Cu(OPiv)_2$	TBHP[c] (2)	DCM	80	PivOH	37
11	$Cu(OPiv)_2$	PIDA[d] (2)	DCM	80	PivOH	28
12	$Cu(OPiv)_2$	O_2	DCM	40	PivOH	22
13	**$Cu(OPiv)_2$**	**O_2**	**DCM**	**80**	**PivOH**	**73**
14	$Cu(OPiv)_2$	O_2	DCM	90	PivOH	44
15	$Cu(OPiv)_2$	O_2	DCM	80	TFA	0
16	$Cu(OPiv)_2$	O_2	DCM	80	TfOH	0
17	$Cu(OPiv)_2$	O_2	DCM	80	AcOH	7

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), catalyst (10 mol%), acid (0.3 mmol), solvent (1.5 mL), 80 °C, O_2 (balloon), >12 h (monitored by TLC).
[b] Yield of the isolated product.
[c] 5.5 M TBHP in decane under argon.
[d] Phenyliodine diacetate.

Table 2 Scope of the Substituted 2-(1*H*-Pyrrol-1-yl)aniline or 2-(1*H*-Pyrrol-1-yl)pyridin-3-amine[a]



[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.9 mmol), $Cu(OPiv)_2$ (10 mol%), PivOH (0.3 mmol), DCM (1.5 mL), 80 °C, under O_2 (balloon) for 12 h.

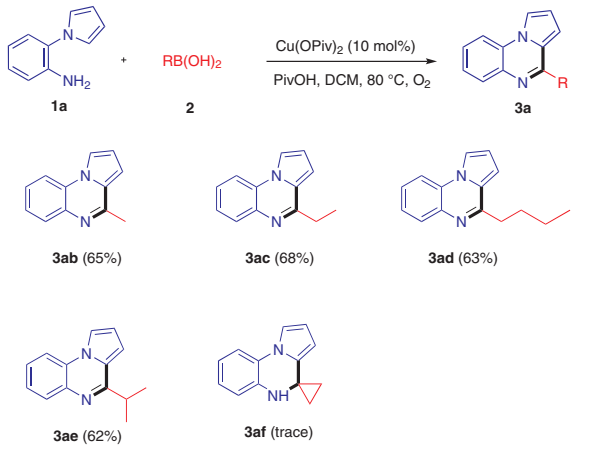
Next, the substrate scope of the alkylboronic acid **2** was investigated under the optimized conditions. As shown in Table 3, the reaction of **1a** with various alkylboronic acids **2** proceeded smoothly and gave the desired products **3ab–ae** in moderate yields. Cyclopropylboronic acid was also inves-

tigated, but unfortunately only a trace of the desired product **3af** was obtained.

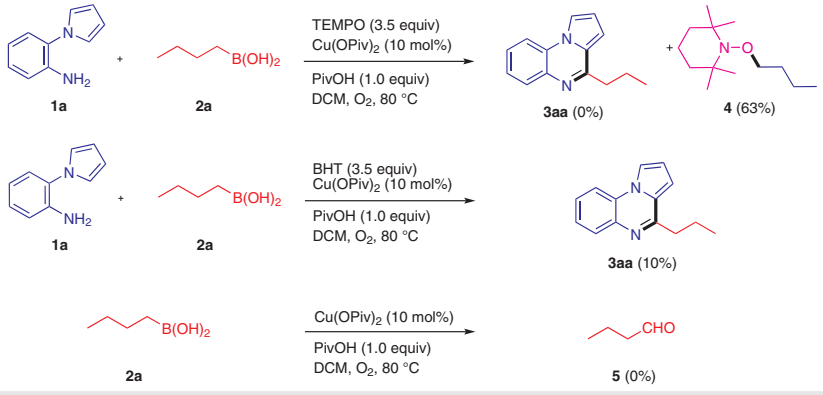
To probe the mechanism of this transformation, we carried out some control experiments (Scheme 2). When 2.0 equivalents of TEMPO were added to the reaction system, none of the desired product was obtained and the alkylated TEMPO **4** was isolated in 63% yield. As expected, on adding 2,6-di-*tert*-butyl-4-methylphenol (BHT) under the standard conditions, **3aa** was obtained in only 10% yield. These results indicate that an alkyl radical formed from substrate **2** is involved in this transformation. When **2a** was added without **1a** under the standard conditions, no butanal (**5**) was detected, proving that the alkyl radical does not react with O_2 to produce butanal.

In light of these experimental results and reports in the literature,[13–15] a possible mechanism is proposed, as shown in Scheme 3. First, the alkyl radical **B** is formed through cleavage of butylboronic acid (**2a**) in the presence of Cu^n. Radical **B** then reacts with **1a** to produce intermediate **C**. Subsequently, the peroxide intermediate **D**, formed from

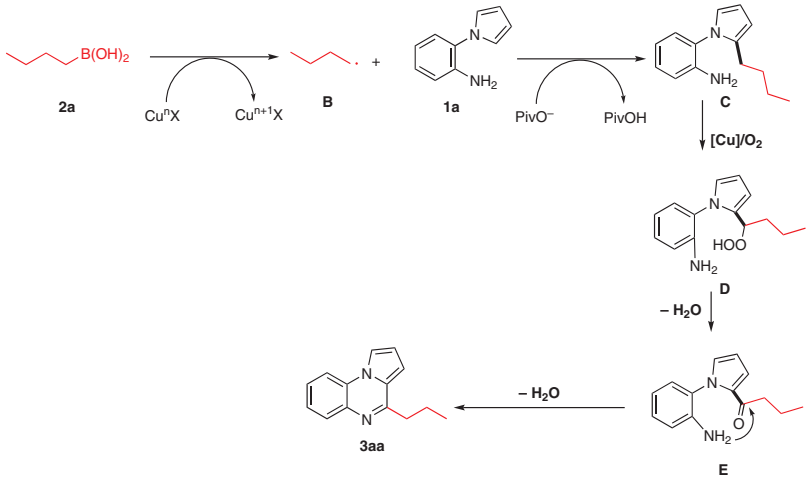
Table 3 Scope of the Alkylboronic Acid[a]



[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.9 mmol), $Cu(OPiv)_2$ (10 mol%), PivOH (0.3 mmol), DCM (1.5 mL), 80 °C, O_2 (balloon), 12 h.



Scheme 2 Control experiments



Scheme 3 Proposed mechanism

compound **C** by Cu-promoted oxidation, decomposes to give intermediate **E**. Finally, intramolecular nucleophilic attack in intermediate **E** leads to the product **3aa**.

In summary, we have developed an effective strategy for synthesizing alkyl-substituted pyrrolo[1,2-*a*]quinoxalines from 2-(1*H*-pyrrol-1-yl)anilines and arylboronic acids.[16] This transformation shows broad functional-group tolerance, and a series of alkyl-substituted pyrrolo[1,2-*a*]quinoxalines can be obtained in moderate to good yields.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610743.

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(16) **4-Propylpyrrolo[1,2-*a*]quinoxaline (3aa):[2] Typical Procedure**
A mixture of 2-(1*H*-pyrrol-1-yl)aniline (**1a**; 1 equiv, 0.3 mmol), $BuB(OH)_2$ (**2a**; 3 equiv, 0.9 mmol), PivOH (1 equiv, 0.3 mmol), $Cu(OPiv)_2$ (10 mol%, 0.03 mmol), and DCM (1 mL) was stirred at 80 °C under O_2 (balloon) for 8 h. Upon completion of the reaction (TLC), the mixture was concentrated in vacuo, and the crude product was purified by column chromatography [silica, gel, PE–EtOAc (10:1)] to give a light-yellow solid; yield: (40.3 mg, 73%); mp 45–46 °C.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.90 (m, 1 H), 7.90–7.89 (m, 1 H), 7.84–7.80 (m, 1 H), 7.49–7.44 (m, 1 H), 7.44–7.39 (m, 1 H), 6.92–6.89 (m, 1 H), 6.85–6.83 (m, 1 H), 3.02–2.97 (m, 2 H), 1.99–1.89 (m, 2 H), 1.10–1.05 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4, 136.0, 129.4, 127.3, 126.8, 126.1, 125.0, 114.1, 113.6, 113.4, 106.3, 37.8, 22.0, 14.3. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{15}N_2$: 211.1230; found: 211.1227.